

**REMARKS**

Claims 1-86 and 88 were previously cancelled. Accordingly, Claims 87 and 89-100 are currently pending.

**Sequence Listing**

In paragraph 2 on page 2 of the Office Action, the Examiner states that SEQ ID NOS: 34 and 43; SEQ ID NOS: 36 and 46; SEQ ID NOS: 51 and 55; and SEQ ID NOS: 53 and 58 are duplicates of each other.

Applicants have deleted SEQ ID NOS: 43, 46, 55 and 58. Thus, sequences beginning at SEQ ID NO: 44 have been renumbered. The specification and claims have been amended to reflect such renumbering of the sequences.

Additionally, Applicants submit a second paper copy and a second computer readable form (computer diskette) of the Sequence Listing with the aforementioned revisions. This Sequence Listing contains SEQ ID NOS 1-55.

Applicants' attorney hereby states that the contents of the second paper copy and the second computer diskette are the same. No new matter is being added by the Sequence Listing. Accordingly, it is respectfully requested that this second Sequence Listing be entered into the application. In addition, this second Sequence Listing has been inserted at the end of the specification.

**Rejection under 35 U.S.C. §112, first paragraph (New Matter)**

Claims 87 and 91-100 are rejected under 35 U.S.C. §112, first paragraph, as allegedly being new matter. In particular, the Examiner alleges that SEQ ID NOS 28 and 32 were not disclosed in the WO/9958680 application and thus are new matter. (Office Action page 2, paragraph 4.)

SEQ ID NO 28 is listed in Figure 4B of the application as filed. This sequence is described on page 6, line 34, of the specification as filed. SEQ ID NO 28 is clone VH EL-25.

SEQ ID NO 32 is listed in Figure 9A of the application as filed. This sequence is described on page 8, line 25, of the specification as filed. SEQ ID NO 32 is a clone B38 deviation designated as DP-15.

Thus, SEQ ID NOS 28 and 32 appear in the figures of the application as filed. Accordingly, Applicants request that the new matter rejection be withdrawn.

**Rejection under 35 U.S.C. §112, first paragraph (Enablement and Written Description)**

Claims 87 and 91-100 are rejected under 35 U.S.C. §112, first paragraph, as allegedly not being fully enabled; and under 35 U.S.C. §112, first paragraph, as allegedly not being fully described in the specification.

Claims 87 and 91-100 (Enablement)

The Examiner specifically states that the specification is enabling for “a polypeptide capable of specific binding to factor VIII and interference with the activity of factor VIII inhibitors...” (Page 2, paragraph 5, of the Office Action.)

However, the Examiner alleges that the specification is not enabled for such a polypeptide comprising a heavy chain variable region of a human antibody with factor VIII specificity and a light chain variable region of a human antibody.

In particular, according to the Examiner:

The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin...Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function. (Office Action page 3, 2<sup>nd</sup> full paragraph.)

The Examiner specifically states that the specification provides “no direction or guidance regarding how to provide any light chain variable region of the claimed antibodies...” (Office Action page 3, 2<sup>nd</sup> full paragraph.)

Applicants respectfully disagree with the Examiner’s analysis. In the present invention, it is shown that only the heavy chain is critical for the activity of the antibody, *i.e.*, the light chain can be varied without affecting the activity of the antibody.

In particular, see Examples 2, 8 and 9 of the specification. These examples describe the isolation of factor VIII binding scFv from phage display libraries for which the variable heavy chain is derived from the immunoglobulin repertoire of a patient with hemophilia A; but the variable light chain is derived from the vector pHEN-VLrep, which contains a variable light chain repertoire of non-immune source. Figures 1, 2, 8 and 10 show that

functional factor VIII binding scFv can be isolated using this protocol. Thus, the specification clearly demonstrates that light chain repertoires derived from non-immunized donors can be used to isolate antigen-specific scFv when combined with a variable heavy chain repertoire of hemophilia A patients with inhibitory antibodies.

Also note the such a scenario is not unique to factor VIII antibodies of the present invention. Accompanying this Amendment are two references showing that only the heavy chain is critical for the activity of the antibody, *i.e.*, the light chain can be varied without affecting the activity of the antibody. These references are Kang et al. *Proc. Natl. Acad. Sci. USA* 88:11120-3 (1991) and Griffin et al. *Blood* 86(12): 4430-6 (1995).

Kang et al. relates to antibody redesign by chain shuffling from random combinatorial immunoglobulin libraries. In the paragraph bridging pages 11122 and 11123, it is stated:

[O]ur results suggest that chain shuffling is an effective route to accessing combinatorial libraries, since once a single antigen binding clone has been identified the family can be readily expanded by shuffling a particular heavy and light chain against a library of light and heavy chains, respectively. Moreover, such shuffling would reach to "optimized" pairing of heavy and light chains for antigen recognition.

Griffin et al. relates to IgG alloantibodies to polymorphic platelet glycoproteins. In the 1<sup>st</sup> full paragraph, in the second column of page 4430, it is stated:

A number of groups have reported on shuffling of immune VH and nonimmune VL genes to produce antibodies that maintain the original immunospecificity. Here, the IgM- and IgG-derived VH gene repertoires from a GPIIIa leu 33-alloimmunized individual were recombined with a nonimmune VL gene repertoire, derived from the lymphocytic mRNA of two nonimmunized human donors, in the phagemid vector pHEN-1-V<sub>Lrep</sub>. Using this approach, we have isolated human monoclonal antibody fragments, specific for the nondenatured leucine form of GPIIIa...

In conclusion, Griffin et al. states "specific human alloantibody fragments can be isolated from V-gene phage display libraries in which only the VH-gene repertoire is derived from an immune source" (3<sup>rd</sup> full paragraph, in the first column of page 4435).

Thus, these references confirm that only the heavy chain is critical for the activity of the antibody. Thus, the specification is enabled for a polypeptide capable of specific binding to factor VIII and interference with the activity of factor VIII inhibitors, which polypeptide comprises a heavy chain variable region of a human antibody with factor VIII specificity and a light chain variable region of a human antibody.

Claims 87 and 91-100 (Written Description)

The Examiner alleges that the claims lack an adequate written description of a polypeptide capable of specific binding to factor VIII and interference with the activity of factor VIII inhibitors, which polypeptide comprises a heavy chain variable region of a human antibody with factor VIII specificity and a light chain variable region of a human antibody. (See Office Action, page 4, paragraph 6.)

Applicants respectfully disagree with the Examiner. The sequences of variable heavy chains are disclosed in the specification. Also, binding of factor VIII to a phage expressing an isolated polypeptide comprising a heavy chain variable region of a human antibody with factor VIII specificity and a light chain variable region of a human antibody is shown in Figure 5. In particular, it is shown for scFv EL-14 containing a variable heavy chain identical to SEQ ID NO 23, and it is shown for scFv IT-2 containing a variable heavy chain identical to SEQ ID NO 25.

The scFv EL-5 clone (containing a variable heavy chain identical to SEQ ID NO 27) and the scFv EL-25 clone (containing a variable heavy chain identical to SEQ ID NO 28) have been derived using the selection protocol described in Examples 1-4. The

results displayed in Figure 1 reveal that these isolated clones bind specifically to the 80 kDa fragment of factor VIII.

ScFv B38 containing a variable heavy region identical to SEQ ID NO 32, scFv B18 containing a variable heavy chain region identical to SEQ ID NO 34, scFv B35 containing a variable heavy chain region identical to SEQ ID NO 36, scFv B04 containing a variable heavy chain region identical to SEQ ID NO 38, are all capable of binding to factor VIII. Figure 8 displays the binding studies of scFv B38, B18 and B35. The binding study of scFv B09 is not displayed in the application but has been determined in an identical manner as shown in Figure 8 for scFv B38, B18 and B35.

ScFv corresponding to clone 34 containing a variable heavy chain region identical to SEQ ID NO 51 and scFv corresponding to clone 41 containing a variable heavy chain region identical to SEQ ID NO 53 were capable of binding to factor VIII as displayed in Figure 10. The amino acid sequences of the variable heavy chain of clone 34 and 41 are depicted in Figure 11.

The manner in which the light chains of the antibodies of the invention are obtained is sufficiently described in the specification. See the enablement discussion above.

Accordingly, the data provided in the specification is sufficient to establish written description. Thus, Applicants respectfully request withdrawal of the written description rejection.

Claims 98-100

The Examiner specifically states that the specification is enabling for a composition capable of specific binding to factor VIII and interference with the activity of factor VIII inhibitors. (Page 2, paragraph 5, of the Office Action.)

However, the Examiner states that the specification is not enabling for pharmaceutical compositions capable of specific binding to factor VIII and interference with the activity of factor VIII inhibitors. (Page 3, 1<sup>st</sup> paragraph, of the Office Action.)

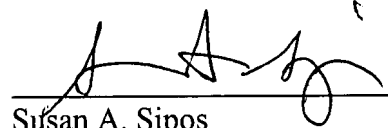
Applicants take this opportunity to refute the remarks on page 4, 2<sup>nd</sup> paragraph, of the Office Action with respect to the declaration by Dr. Voorberg, filed January 23, 2007. The Giles et al. publication (Giles et al. *Thromb. Haemost.* 1998; 79: 872-5) does show that results from *in vitro* experiments as measured by the functional Bethesda assay correlate with *in vivo* data. Also, clinical decisions are made based on the results of *in vitro* assays. Thus, it follows that, based on the results of inhibitor neutralization presented in the specification, a person having ordinary skill in the art would be able to practice the claimed invention.

Nevertheless, to expedite prosecution, Claims 98-100 have been amended to delete the term "pharmaceutical." Thus, the rejection is obviated.

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For the above reasons, allowance of the pending claims is earnestly requested. If the Examiner has any questions regarding this amendment, he is invited to contact the undersigned at the telephone number listed below.

Respectfully submitted,

A handwritten signature in black ink, appearing to read 'Susan A. Sipos', is written over a horizontal line.

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